PATENT COOPERATION TREATY

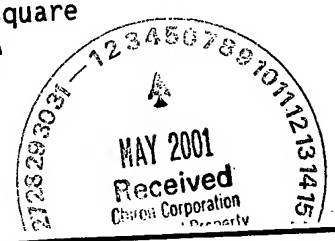
PCT

From the INTERNATIONAL SEARCHING AUTHORITY

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
CARPMAELS & RANSFORD
Attn. HALLYBONE, H.G.
43 Bloomsbury Square
London WC1A 2RA
UNITED KINGDOM



Applicant's or agent's file reference: P023016WO	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No.: PCT/IB 00/01440	International filing date (day/month/year): 28/09/2000
Applicant: CHIRON S.P.A. et al.	

Date of mailing (day/month/year): 06/04/2001

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority: European Patent Office, P.B. 5818 Patentlaan 2, NL-2280 HV Rijswijk, Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer: Barbara Klaver

DOCKETED on/by 5/4/01 / Atty. AAH PA File # PP016510.101 Due Date _____ Ext _____

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
P023016WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB 00/01440	28/09/2000	29/09/1999
Applicant		
CHIRON S.P.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 00/01440

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte. ional Application No
PCT/IB 00/01440

A. CLASSIFICATION OF SUBJECT MATTE
IPC 7 A61K39/116 A61K39/39 A61K39/106 A61K39/108 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 21950 A (MEDEVA HOLDINGS BV ;ROBERTS MARK (GB); DOUGAN GORDON (GB)) 11 November 1993 (1993-11-11) page 4, line 15 -page 6, line 2 page 8, line 20 -page 9, line 8 claims 1-5,11-14,17-19 ---	1,3,7-13
X	US 5 182 109 A (AIZAWA CHIKARA ET AL) 26 January 1993 (1993-01-26) column 1, line 36 - line 43 column 2, line 29 - line 61 column 8, line 51 -column 9, line 10 examples 5,15 claims 1-4 --- -/--	1,3,8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 2001	06/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stein, A

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDER[illegible]ABE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RYAN E ET AL: "The adjuvant action of mutants of the heat labile toxin of E. coli for a nasally delivered acellular pertussis vaccine." IMMUNOLOGY LETTERS, vol. 69, no. 1, 15 June 1999 (1999-06-15), page 59 XP000982713 10th International Congress of Mucosal Imunology;Amsterdam, Netherlands; June 27-July 1, 1999 ISSN: 0165-2478 the whole document	1-6,8-13
Y	DEL GIUDICE GIUSEPPE ET AL: "Molecular basis of vaccination." MOLECULAR ASPECTS OF MEDICINE, vol. 19, no. 1, February 1998 (1998-02), pages 1-70, XP002162795 ISSN: 0098-2997 cited in the application page 23, line 29 -page 25, line 15 page 30, line 5 - line 9; table 2 page 33, line 8 -page 36, line 13 page 43, line 11 -page 46, line 39	1-6,8-13
A	EP 0 462 534 A (SCLAVO SPA) 27 December 1991 (1991-12-27) page 3, line 30 -page 4, line 45 page 14, line 1 - line 43; table X claims 1-6,13,14	1-11
A	WO 97 02348 A (GIANNELLI VALENTINA ;PIZZA MARIAGRAZIA (IT); BIOCINE SPA (IT); RAP) 23 January 1997 (1997-01-23) page 1, line 5 - line 16 page 6, line 33 -page 7, line 2 page 8, line 20 -page 9, line 13 page 47, line 23 -page 49, line 22 claims 1,4,10,11	2,12,13
P,X	RYAN ELIZABETH J ET AL: "Mutants of Escherichia coli heat-labile toxin act as effective mucosal adjuvants for nasal delivery of an acellular pertussis vaccine: Differential effects of the nontoxic AB complex and enzyme activity on Th1 and Th2 cells." INFECTION AND IMMUNITY, vol. 67, no. 12, December 1999 (1999-12), pages 6270-6280, XP002162796 ISSN: 0019-9567 the whole document	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 00/01440

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9321950 A	11-11-1993	AT	186218 T	15-11-1999
		AU	4267093 A	29-11-1993
		DE	69326948 D	09-12-1999
		DE	69326948 T	16-03-2000
		DK	639081 T	10-04-2000
		EP	0639081 A	22-02-1995
		EP	0937462 A	25-08-1999
		ES	2141765 T	01-04-2000
		GR	3032381 T	27-04-2000
		PT	639081 T	28-04-2000
US 5182109 A	26-01-1993	JP	2243633 A	27-09-1990
		JP	2849632 B	20-01-1999
		CA	1335571 A	16-05-1995
		DE	3911442 A	02-11-1989
		FR	2629717 A	13-10-1989
		GB	2217600 A,B	01-11-1989
		KR	9603378 B	09-03-1996
EP 0462534 A	27-12-1991	IT	1248735 B	26-01-1995
		CA	2045071 A	22-12-1991
		JP	2690215 B	10-12-1997
		JP	4368337 A	21-12-1992
WO 9702348 A	23-01-1997	AU	6238896 A	05-02-1997
		EP	0835314 A	15-04-1998

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: P023016WO: HGH

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/IB00/01440	28/09/2000	29/09/1999

Title of invention: MUCOSAL DTPa VACCINES

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CHIRON SpA
VIA FIORENTINA 1
53100 SIENA
ITALY

Telephone No.
Facsimile No.
Teleprinter No.
Applicant's registration No. with the Office

State *(that is, country)* of nationality: IT
State *(that is, country)* of residence: IT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAPPUOLI Rino
CHIRON SpA
VIA FIORENTINA 1
53100 SIENA
ITALY

State *(that is, country)* of nationality: IT
State *(that is, country)* of residence: IT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PIZZA, Mariagrazia
CHIRON SpA
VIA FIORENTINA 1
53100 SIENA
ITALY

State *(that is, country)* of nationality: IT
State *(that is, country)* of residence: IT

☐ Further applicants are indicated on a continuation sheet.

See Notes to the demand form

International application No. PCT/IB00/01440

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☑ agent ☐ common representative

and ☑ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HALLYBONE, Huw George
CARPMAELS & RANSFORD
43 BLOOMSBURY SQUARE
LONDON WC1A 2RA
GB

Telephone No. 020 7242-8692

Facsimile No. 020 7405-4166

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination **to start on the basis of:**

☑ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination **to be postponed** until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

☑ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes **not to elect:**

See Notes to the demand form

Sheet No. 3

International application No. PCT/IB00/01440

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

P. O'Howard HOWARD, Paul Nicholas

for HALLYBONE, Huw George

Authorised Representative

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/IB00/01440	For International Preliminary Examining Authority use only
Applicant's or agent's file reference P023016WO: HGH	Date stamp of the IPEA
Applicant CHIRON SpA	

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	EUR 1,533	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	EUR 147	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1,680	TOTAL	

MODE OF PAYMENT

- [x] authorization to charge deposit account with the IPEA (see below)
- [ ] cheque
- [ ] postal money order
- [ ] bank draft
- [ ] cash
- [ ] revenue stamps
- [ ] coupons
- [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EP

- [x] Authorization to charge the total fees indicated above.
- [x] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 2805.0059

Date: 23rd April 2001

Name: CARPMAELS & RANSFORD

Signature: Carpmaels & Ransford

See Notes to the fee calculation sheet

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
HALLYBONE, Huw George et al
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	31.07.2001
Applicant's or agent's file reference: P023016WO	**REPLY DUE** **within 3 month(s)** from the above date of mailing
International application No.: PCT/IB00/01440	International filing date *(day/month/year)*: 28/09/2000
Priority date *(day/month/year)*: 29/09/1999	
International Patent Classification (IPC) or both national classification and IPC: A61K39/00	
Applicant: CHIRON S.P.A. et al.	

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29/01/2002.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Herrero, M

Formalities officer (incl. extension of time limits)
Digiusto, M
Telephone No. +49 89 2399 8162

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-12 as originally filed

Claims, No.:

1-13 as originally filed

Drawings, sheets:

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 8-10 with respect to industrial applicability,

because:

☒ the said international application, or the said claims Nos. 8-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
Novelty (N) Claims 1, 3, 7-13

Inventive step (IS) Claims 1-13

Industrial applicability (IA) Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION III

Claims 8-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (i.e. methods of treatment of the human or animal body by therapy). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The document Infect. Immun. **67**:6270-6280 indicated in the International Search Report as a P-document (published on December 1999) is not to be regarded as state of the art according to Rule 64 (1) PCT, as the date of priority claimed (29.09.99) can be allowed for the relevant parts of the present application.

2.2 Reference is made to the following documents:

D1: WO 93/21950
D2: Ryan, E.J. et al (15.06.99) Immunology Letters **69**:59
D3: Del Guidice, G. et al (1998) Molecular Aspects of Medicine **19**:1-70 (also cited in the application).

2.3 Novelty and inventive step (Art. 33(2) and (3) PCT)

The present application does not satisfy the criteria set forth in Article 33(2) and (3) PCT because,

a) the subject-matter of Claims 1, 3 and 7-13 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT)

b) the subject-matter claimed does not involve an inventive step (Rule 65(1)(2) PCT).

D1 describes vaccine compositions for mucosal (intranasal or oral) delivery comprising the acellular pertussis antigens pertactin and filamentous haemagglutinin (FHA), tetanus toxin C fragment and a non-toxic immunogenic form of diphtheria toxin, in which the mucosal immunogenicity of the mixture of antigens may be enhanced by incorporating genetically detoxified variants of cholera toxin or *E. coli* heat-labile toxin as mucosal adjuvants, thereby providing a mucosal diphtheria-tetanus-pertussis (DTP) vaccine. Additionally this vaccine could contain immunogenic forms of e.g. *Haemophilus influenzae* group B polysaccharide (HiB), thereby providing a DTPHib vaccine (cf page 8, lines 20-28 bridging over page 9, lines 1-8 in view of page 2, lines 10-18, Claim 17). The vaccines of D1 may be administered in several doses (cf page 11, lines 2-6).

Under their generic formulation the mucosal DTPa vaccines of Claims 1, 3 and 7, the composition of Claim 11, the therapeutic methods according to Claims 8-10 and the medical uses recited in Claims 12-13 appear to be neither novel nor inventive over the disclosures of D1, contrary to the requirements of Art. 33(2) and (3) PCT.

D2 reports that in a murine model for infection with *Bordetella pertussis*, nasally delivered acellular pertussis vaccines formulated with the *E. coli* heat labile toxin mutants LTK63 and LTR72 as adjuvants, confer a high level of protection against respiratory challenge. D2 analyses the distinguishing features of the adjuvant action of each one of LTK63 and LTR72 mutants and concludes that the obtained results suggest that LT mutants enhance antigen presentation and innate immune responses and thereby augment acquired immunity at a mucosal surface.

Among other relevant teachings D3 reviews the composition of acellular pertussis vaccines studied in efficacy trials, including the combination PT-9K/129G + FHA + pertactin + diphtheria and tetanus toxoids (see especially page 30, Table 2 and page 33 last paragraph bridging over pages 34 and 36). Concerning diphtheria antigens of interest D3 proposes the use of the CRM197 mutant as alternative for diphtheria toxoid (see page 23, last paragraph bridging over page 25, paragraphs 1-2). The possible application of CT and LT mutants as mucosal adjuvants in mucosally delivered vaccines for human use is analysed on pages 37-46. The

particular expected advantages associated with the use of either the LTR72 mutant (which retains a residual enzymatic activity and toxicity *in vitro* and *in vivo*) or the LTK63 mutant (which is totally devoid of toxicity) as mucosal adjuvants of existing vaccines are apparent from the detailed information presented on pages 43, 45 and 46.

In the light of the technical problem underlying the present application, i.e. the provision of an effective mucosal DTPa combination vaccine, the subject-matter hereby claimed (i.e. Claims 1 to 13) seems to be rendered obvious to the person skilled in the art from the direct combination of teachings of D2 and D3, referred to above. In this regard it is noted that the skilled person was aware of the existence of murine models for protection of immunized mice against infection with *Bordetella pertussis* which can be correlated with vaccine efficacy in human clinical trials, e.g. the respiratory challenge model referred to on page 8, lines 2-5 of the present application. Therefore the inventive step requirements of Art. 33(3) PCT would not appear to be met by any of present Claims 1 to 13.

2.4 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present Claims 8-10 and 12-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2.5 It is not at present apparent which part of the application could serve as a basis for a new claim which would satisfy the criteria set forth in Article 33(1) PCT. Should the Applicant nevertheless regard some particular matter as suitable an independent claim including such particular matter should be filed taking account of Rule 6.3(b) PCT. The applicant should also indicate in the letter of reply the difference vis-à-vis the state of the art (especially D2 and D2+D3) and the significance thereof.

2.6 The applicant is requested to file amendments by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate.

Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

2.7 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

2.8 Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply rather than be incorporated into the application, Article 34(2)(b) PCT.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

2. The expression "hereby incorporated by reference" in respect of prior art documents on page 1, line 2 leads to a doubt as to whether the requirements of the description being self-contained are satisfied (see PCT Guidelines C-II, 4-17).

SECTION VIII

1. Insofar as the subject-matter presently claimed relies on the use of a detoxified form of cholera toxin, neither the requirements of Art. 6 PCT nor Art. 5 PCT appear to be met, since the corresponding embodiments are neither adequately supported in the description nor sufficiently disclosed by means of suitable information of a technical nature.

2. Independent Claim 11 should have indicated that the resulting composition was intended "... for use as a mucosal DTPa vaccine" (under its present wording Claim 11 is not unitary with Claim 1).

3. The statement in the description on page 11, lines 10-11 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HALLYBONE, Huw George et al
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	10.10.2001
Applicant's or agent's file reference: P023016WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/01440	28/09/2000	29/09/1999

Applicant: CHIRON S.P.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Digiusto, M

Tel.+49 89 2399-8162

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P023016WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB00/01440	28/09/2000	29/09/1999
International Patent Classification (IPC) or national classification and IPC		
A61K39/00		
Applicant		
CHIRON S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/04/2001	10.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Herrero, M Telephone No. +49 89 2399 8542

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB00/01440

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-12 as originally filed

Claims, No.:

1-13 as originally filed

Drawings, sheets:

1/15-15/15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 8-10 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 8-10 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 2, 4-6

	No:	Claims	1, 3, 7-13
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-7, 11-13
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

SECTION I

6. Additional observations:

This preliminary examination report also takes into account the Applicants' letter dated 24.09.01.

SECTION III

Claims 8-10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT (i.e. methods of treatment of the human or animal body by therapy). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

2. CITATIONS AND EXPLANATIONS

2.1 The document Infect. Immun. **67**:6270-6280 indicated in the International Search Report as a P-document (published on December 1999) is not to be regarded as state of the art according to Rule 64 (1) PCT, as the date of priority claimed (29.09.99) can be allowed for the relevant parts of the present application.

2.2 The following documents have been considered for the purposes of this report:

D1: WO 93/21950
D2: Ryan, E.J. et al (15.06.99) Immunology Letters **69**:59
D3: Del Guidice, G. et al (1998) Molecular Aspects of Medicine **19**:1-70 (also cited in the application).

2.3 Novelty and inventive step (Art. 33(2) and (3) PCT)

The present application does not satisfy the criteria set forth in Article 33(2) and (3) PCT because,

a) the subject-matter of Claims 1, 3 and 7-13 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT)

b) the subject-matter claimed does not involve an inventive step (Rule 65(1)(2) PCT).

D1 describes vaccine compositions for mucosal (intranasal or oral) delivery comprising the acellular pertussis antigens pertactin and filamentous haemagglutinin (FHA), tetanus toxin C fragment and a non-toxic immunogenic form of diphtheria toxin, in which the mucosal immunogenicity of the mixture of antigens may be enhanced by incorporating genetically detoxified variants of cholera toxin or *E. coli* heat-labile toxin as mucosal adjuvants, thereby providing a mucosal diphtheria-tetanus-pertussis (DTP) vaccine. Additionally this vaccine could contain immunogenic forms of e.g. *Haemophilus influenzae* group B polysaccharide (HiB), thereby providing a DTPHib vaccine (cf page 8, lines 20-28 bridging over page 9, lines 1-8 in view of page 2, lines 10-18, Claim 17). The vaccines of D1 may be administered in several doses (cf page 11, lines 2-6).

Under their generic formulation the mucosal DTPa vaccines of Claims 1, 3 and 7, the composition of Claim 11, the therapeutic methods according to Claims 8-10 and the medical uses recited in Claims 12-13 appear to be neither novel nor inventive over the disclosures of D1, contrary to the requirements of Art. 33(2) and (3) PCT.

D2 reports that in a murine model for infection with *Bordetella pertussis*, nasally delivered acellular pertussis vaccines formulated with the *E. coli* heat labile toxin mutants LTK63 and LTR72 as adjuvants, confer a high level of protection against respiratory challenge. D2 analyses the distinguishing features of the adjuvant action of each one of LTK63 and LTR72 mutants and concludes that the obtained

results suggest that LT mutants enhance antigen presentation and innate immune responses and thereby augment acquired immunity at a mucosal surface.

Among other relevant teachings D3 reviews the composition of acellular pertussis vaccines studied in efficacy trials, including the combination PT-9K/129G + FHA + pertactin + diphtheria and tetanus toxoids (see especially page 30, Table 2 and page 33 last paragraph bridging over pages 34 and 36). Concerning diphtheria antigens of interest D3 proposes the use of the CRM197 mutant as alternative for diphtheria toxoid (see page 23, last paragraph bridging over page 25, paragraphs 1-2). The possible application of CT and LT mutants as mucosal adjuvants in mucosally delivered vaccines for human use is analysed on pages 37-46. The particular expected advantages associated with the use of either the LTR72 mutant (which retains a residual enzymatic activity and toxicity *in vitro* and *in vivo*) or the LTK63 mutant (which is totally devoid of toxicity) as mucosal adjuvants of existing vaccines are apparent from the detailed information presented on pages 43, 45 and 46.

In the light of the technical problem underlying the present application, i.e. the provision of an effective mucosal DTPa combination vaccine, the subject-matter hereby claimed (i.e. Claims 1 to 13) seems to be rendered obvious to the person skilled in the art from the direct combination of teachings of D2 and D3, referred to above. In this regard it is noted that the skilled person was aware of the existence of murine models for protection of immunized mice against infection with *Bordetella pertussis* which can be correlated with vaccine efficacy in human clinical trials, e.g. the respiratory challenge model referred to on page 8, lines 2-5 of the present application. Therefore the inventive step requirements of Art. 33(3) PCT would not appear to be met by any of present Claims 1 to 13.

2.4 Industrial applicability (Art. 33(4) PCT)

For the assessment of the present Claims 8-10 and 12-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but

may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

SECTION VII

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

2. The expression "hereby incorporated by reference" in respect of prior art documents on page 1, line 2 leads to a doubt as to whether the requirements of the description being self-contained are satisfied (see PCT Guidelines C-II, 4-17).

SECTION VIII

1. Insofar as the subject-matter presently claimed relies on the use of a detoxified form of cholera toxin, neither the requirements of Art. 6 PCT nor Art. 5 PCT appear to be met, since the corresponding embodiments are neither adequately supported in the description nor sufficiently disclosed by means of suitable information of a technical nature.

2. Independent Claim 11 should have indicated that the resulting composition was intended "... for use as a mucosal DTPa vaccine" (under its present wording Claim 11 is not unitary with Claim 1).

3. The statement in the description on page 11, lines 10-11 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P023016WO

Box No. I TITLE OF INVENTION

MUCOSAL DTPa VACCINES

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CHIRON SpA
Via Fiorentina 1,
53100 Siena,
ITALY.

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: ITALY

State *(that is, country)* of residence: ITALY

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RAPPUOLI Rino,
CHIRON SpA,
Via Fiorentina 1,
53100 Siena,
ITALY.

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: ITALY

State *(that is, country)* of residence: ITALY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HALLYBONE, Huw George,
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Telephone No. +44 20-7242 8692

Facsimile No. +44 20-7405 4166

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No. 2......

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address	This person is
Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)* PIZZA, Mariagrazia, CHIRON SpA, Via Fiorentina 1, 53100 Siena, ITALY.	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)*
State *(that is, country)* of nationality: ITALY	State *(that is, country)* of residence: ITALY

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address	This person is
Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)*
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address	This person is
Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)*
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address	This person is
Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only *(If this check-box is marked, do not fill in below.)*
State *(that is, country)* of nationality:	State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☐ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☐ **AE** United Arab Emirates
- ☐ **AG** Antigua and Barbuda
- ☐ **AL** Albania .....
- ☐ **AM** Armenia .....
- ☐ **AT** Austria .....
- ☐ **AU** Australia .....
- ☐ **AZ** Azerbaijan
- ☐ **BA** Bosnia and Herzegovina .....
- ☐ **BB** Barbados
- ☐ **BG** Bulgaria .....
- ☐ **BR** Brazil .....
- ☐ **BY** Belarus .....
- ☐ **BZ** Belize
- ☒ **CA** Canada
- ☐ **CH and LI** Switzerland and Liechtenstein
- ☐ **CN** China .....
- ☐ **CR** Costa Rica .....
- ☐ **CU** Cuba .....
- ☐ **CZ** Czech Republic .....
- ☐ **DE** Germany .....
- ☐ **DK** Denmark .....
- ☐ **DM** Dominica
- ☐ **DZ** Algeria .....
- ☐ **EE** Estonia .....
- ☐ **ES** Spain .....
- ☐ **FI** Finland .....
- ☐ **GB** United Kingdom
- ☐ **GD** Grenada
- ☐ **GE** Georgia .....
- ☐ **GH** Ghana .....
- ☐ **GM** Gambia
- ☐ **HR** Croatia .....
- ☐ **HU** Hungary .....
- ☐ **ID** Indonesia
- ☐ **IL** Israel .....
- ☐ **IN** India .....
- ☐ **IS** Iceland
- ☒ **JP** Japan .....
- ☐ **KE** Kenya .....
- ☐ **KG** Kyrgyzstan .....
- ☐ **KP** Democratic People's Republic of Korea .....
- ☐ **KR** Republic of Korea .....
- ☐ **KZ** Kazakhstan .....
- ☐ **LC** Saint Lucia
- ☐ **LK** Sri Lanka
- ☐ **LR** Liberia
- ☐ **LS** Lesotho .....
- ☐ **LT** Lithuania
- ☐ **LU** Luxembourg
- ☐ **LV** Latvia
- ☐ **MA** Morocco .....
- ☐ **MD** Republic of Moldova .....
- ☐ **MG** Madagascar .....
- ☐ **MK** The former Yugoslav Republic of Macedonia .....
- ☐ **MN** Mongolia
- ☐ **MW** Malawi .....
- ☐ **MX** Mexico .....
- ☐ **MZ** Mozambique
- ☐ **NO** Norway
- ☐ **NZ** New Zealand .....
- ☐ **PL** Poland .....
- ☐ **PT** Portugal .....
- ☐ **RO** Romania
- ☐ **RU** Russian Federation .....
- ☐ **SD** Sudan
- ☐ **SE** Sweden
- ☐ **SG** Singapore
- ☐ **SI** Slovenia .....
- ☐ **SK** Slovakia .....
- ☐ **SL** Sierra Leone .....
- ☐ **TJ** Tajikistan .....
- ☐ **TM** Turkmenistan .....
- ☐ **TR** Turkey .....
- ☐ **TT** Trinidad and Tobago .....
- ☐ **TZ** United Republic of Tanzania
- ☐ **UA** Ukraine .....
- ☐ **UG** Uganda .....
- ☒ **US** United States of America .....
- ☐ **UZ** Uzbekistan .....
- ☐ **VN** Viet Nam .....
- ☐ **YU** Yugoslavia .....
- ☐ **ZA** South Africa .....
- ☐ **ZW** Zimbabwe .....

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplem[redacted] Box is not used, this sheet should not be included i[redacted] request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. IV

DE MINVIELLE DEVAUX, Ian Benedict Peter
CARPMAEL, John William Maurice
JONES, Alan John
COLGAN, Stephen James
HOWICK, Nicholas Keith
FISHER, Adrian John
MERCER, Christopher Paul
HALLYBONE, Huw George
JACKSON, Richard Eric
HOWARD, Paul Nicholas
JAMES, Anthony Christopher W.P.

also of CARPMAELS & RANSFORD, 43 Bloomsbury Square, London WC1A 2RA, United Kingdom

Box No. VI PRIORITY CLAIM ☐ Further priority claims a[illegible]cated in the Supplemental Box:

Filing date of earlier application (day/month/year)	[illegible]mber of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 29th September 1999 (29.09.99)	9923060.9	GB		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s):

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*: ISA /

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 5
description (excluding sequence listing part)	: 12
claims	: 1
abstract	: 1
drawings	: 15
sequence listing part of description	:
Total number of sheets	: 34

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract: 8

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

HALEYBONE, Huw George

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference P023016WO

Applicant
CHIRON SPA

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . £55 T

2. SEARCH FEE . . . . . S

International search to be carried out by _____
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee
The international application contains _____ sheets.

first 30 sheets b1

_____ x _____ = b2
remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B . . . . B

Designation Fees
The international application contains _____ designations.

_____ x _____ = D
number of designation fees payable *(maximum 8)* amount of designation fee

Add amounts entered at B and D and enter total at I I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . P

5. TOTAL FEES PAYABLE . . . . . £55 TOTAL

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☒ authorization to charge deposit account (see below)	☐ bank draft	☐ coupons
☐ cheque	☐ cash	☐ other *(specify):*
☐ postal money order	☐ revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____ ☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

D00019 — Deposit Account No.

22.09.2000 — Date *(day/month/year)*

Signature

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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PCT

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9923060.9 29 September 1999 (29.09.1999) GB

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **RAPPUOLI, Rino** [IT/IT]; Chiron S.p.A., Via Fiorentina, 1, I-53100 Siena (IT). **PIZZA, Mariagrazia** [IT/IT]; Chiron S.p.A., Via Fiorentina, 1, I-53100 Siena (IT).

(74) Agents: **HALLYBONE, Huw, George** et al.; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

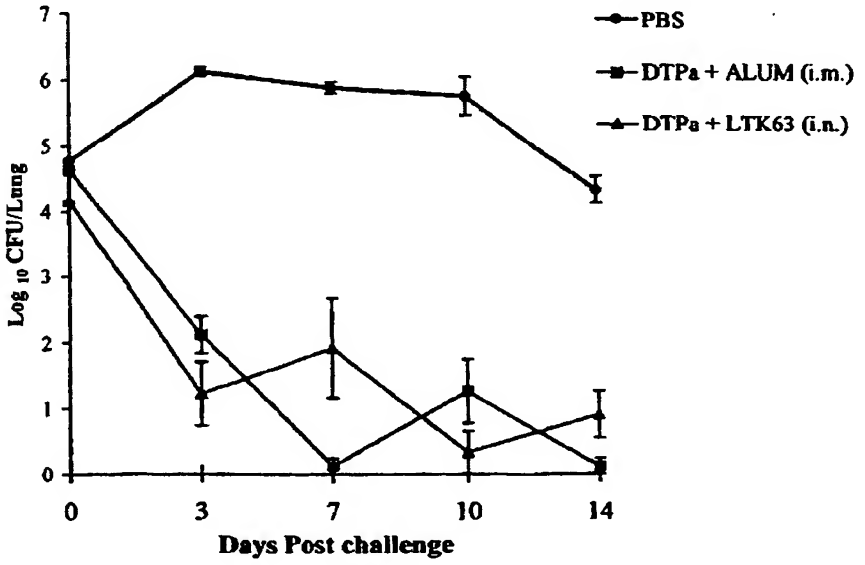
(81) Designated States *(national)*: CA, JP, US.

(84) Designated States *(regional)*: European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MUCOSAL DTPa VACCINES



(57) Abstract: Mucosal DTPa vaccines, especially intranasal vaccines, comprising (a) a diphtheria antigen, a tetanus antigen and an acellular pertussis antigen, and (b) a detoxified mutant of cholera toxin (CT) or *E.coli* heat labile toxin (LT). Component (b) acts as a mucosal adjuvant. The acellular pertussis antigen preferably comprises pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) and, optionally, pertactin. The mucosally-delivered combined DTPa formulation is capable of generating a level of protection against *B.pertussis* infection equivalent to that observed by alum-adjuvanted parenteral administration.

WO 01/22993 A2